REMARKS

STATUS OF THE CLAIMS

Claims 1-4, 6-11, 14, and 17-19 and 21-33 were pending. Claim 1 has been amended to specify that the backbone regions of each zinc finger are not derived from Zif268 or TFIIIA, as described throughout the specification, for example, on page 10, lines 10 to 16 (defining "backbone") and the Background and page 7, lines 1-2 (indicating that the claimed molecules are unlike previously described ZFPs whose backbone regions are derived from Zif268 or TFIIIA). Claim 21 has also been amended as shown above to remove any issues about antecedent basis. Thus, claims 1-4, 6-11, 14, and 17-19 and 21-33 are pending as shown above.

RESTRICTION REQUIREMENT

Applicants' traversal of the Restriction Requirement has been deemed unpersuasive and the Restriction Requirement made FINAL. (Office Action, pages 2-4).

Applicants note again that this was a restriction requirement rather than an election of species requirement. Thus, it remains improper inasmuch as restriction as between the various functional domains of a dependent claim is untenable. In particular, the Examiner errs in asserting that a separate search is required for each functional domain separately from the modified plant zinc finger protein of the independent claim. *See,* Office Action, page 4. In point of fact, a search of the art for a protein comprising any modified plant zinc finger protein would necessarily and inevitably reveal all such proteins containing attached functional domains. As noted in M.P.E.P. § 803.02, restriction as between related members of a Markush Group is improper (emphasis added):

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they may be directed to independent and distinct inventions. In such a case, the examiner will not follow the procedure described below and will not require provisional election of a single species.

Thus, because the search and examination of the entire scope of claims 14 and 33 can be made without serious burden, the restriction requirement should be withdrawn.[1]

35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Claims 1-4, 6-11, 14, and 17-19 and 21-33 were rejected as allegedly not described in the specification as filed in such a way as to reasonably convey to the skilled artisan that applicants were in possession of the claimed subject matter. (Office Action, pages 3-6). In particular, it was alleged with respect to claim 1 that "the claim does not specify in what way the amino acid sequence of the claimed protein has been 'modified.'" (Office Action, page 5). With regard to claim 21, it was alleged that modified plant zinc finger proteins in which the "only modification made is the alteration of the amino acid sequence of the recognition region are not adequately described." *Id.* Furthermore, it is alleged that the as-filed specification does not describe modified plant zinc finger proteins including non-canonical zinc fingers "as the specification describes only a single genus of polynucleotides," namely a tandem array of three modified canonical zinc fingers, two derived from *Arabidopsis* and one from petunia. *Id.*

As a threshold matter, and contrary to the Examiner's assertions regarding claim 1, Applicants note that independent claim 1 does in fact specify in what ways the amino acid sequence of the claimed protein has been modified. In particular, claim 1 requires: (1) that the modified plant zinc finger include a tandem array of zinc fingers[2], (2) that the backbone regions of these tandem arrays be separated by between 5 and 50 amino acids, (3) that the backbone regions are not derived from Zif268 or TFIIIA and (4) that zinc fingers are engineered to bind to a target site. Thus, when properly construed, claim 1 (and claims dependent therefrom) clearly specify the modifications as compared to naturally occurring plant zinc finger proteins.

Turning to the assertion that the subject matter of claim 21 (modified plant zinc finger proteins in which the recognition region is modified) is not adequately described, Applicants direct the Examiner's attention to the following passages where the non-plant structure of the

[1] Should the Examiner withdraw the restriction requirement and instead apply an election of species requirement as between allegedly distinct species, Applicants again note that a search of the art for modified plant zinc finger proteins in combination with any functional domain recited in claims 14 and 33 would necessarily and inevitably reveal references relevant to the other functional domains. Thus, neither restriction nor election is proper.

[2] Thus reciting that the inter-finger distance typical of a plant zinc finger protein has been shortened, inasmuch as naturally-occurring plant zinc fingers do not occur in tandem arrays (*See* Office Action at page 5, lines 8-11)

claimed modified zinc finger proteins is clearly indicated to include embodiments in which only the recognition regions are modified as compared to naturally occurring plant zinc finger proteins (page 8, lines 2-13 and page 20, lines 1-7, emphasis added):

> In the latter case, **plant sequences are used preferably in all regions except those residues involved in recognition and/or binding to the target site, which can comprise, for example, sequences obtained by rational design and/or selection**.
>
> It will be readily apparent that various combinations of zinc fingers can be used in a single modified plant ZFP. **For example, all of the finger components can be designed (i.e., their sequences are obtained as a result of rational design methods); all of the finger components can be selected (i.e., their sequences are obtained by a selection method such as, e.g. phage display, two-hybrid systems or interaction trap assays); all of the finger components can be naturally-occurring plant zinc fingers; or the component fingers of a modified plant ZFP can be any combination of naturally-occurring plant zinc fingers, designed fingers and selected fingers.**

> Optionally, modified plant ZFPs can include one or more residues not present in a naturally occurring plant zinc finger such as can be obtained by, for example, design and/or selection. **For example, one or more sequence in the alpha-helical region, particularly residues involved in target-recognition (e.g., amino acids -1, +2, +3 and +6), can be altered with respect to a naturally occurring plant ZFP.** Any recognition sequence can be chosen, for example, by selecting residues known to bind to certain target sequences, determined as described herein and in the references cited herein.

Plainly, the as-filed specification contains literal description of the subject matter of claim 21, in which the "only" modification as compared to a naturally occurring plant zinc finger protein is modification of the recognition region of the zinc fingers.

Thus, Applicants submit that the Examiner errs in asserting that Applicants have only described the particular sequences exemplified in the specification. In fact, both non-canonical and canonical zinc fingers are amply described in the specification as filed (including original claims). Indeed, disclosure, much less exemplification, of multiple embodiments has never been

a legal requirement of 35 U.S.C. § 112, first paragraph and, in fact, the Federal Circuit, the Board, the M.P.E.P. and the PTO's own Training Materials forbid such a test.[3]

Here, the as-filed specification contains clear literal description of zinc finger proteins (*see, e.g.,* the entire Background section and page 16, line 26 to page 18, line 17); canonical zinc fingers (*see, e.g.,* page 1, line 24 to page 2, line 16 and page 19, lines 7-10); non-canonical zinc fingers (*see, e.g.,* page 2, lines 17-19; page 10, line 25 through page 11, line 2 and page 19, lines 7-13); as well as methods of altering the recognition regions of these canonical and non-canonical zinc fingers (*see, e.g.,* page 11, lines 3-16; page 20, lines 1-7 and page 20, lines 23-28). Moreover, detailed description is also present in the as-filed specification regarding the claimed proteins *per se* (*see, e.g.,* Examples).

Thus, it is plain that Applicants were in possession of the claimed subject matter at the time of filing. To require literal description of actual, multiple embodiments is contrary to all established precedent.

Indeed, the Examiner has ignored the well-established rule that an applicant need not describe and preferably omits that which is not new. As set forth recently in *Capon v. Eshhar* 76 USPQ2d 1078 (Fed. Cir. 2005), the Federal Circuit completely rejects the notion that the specification must describe information that is either known or can readily be determined based on scientific facts (*Capon* at page 1085, emphasis added):

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. ...
>
> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

[3] As the Examples of PTO Training Materials on Written Description, including Example 14: "Product by Function," make clear, disclosure of even a single species can readily satisfy the written description requirement for broad claims.

The holding in *Capon* in particularly relevant to the instant case because the fact pattern in *Capon* is highly analogous to the fact pattern in the case at issue. In *Capon*, the Federal Circuit held that the precise sequence of a chimeric (fusion) antibody need **not** be described because the components were well known. Examiner's assertion in the instant case that Applicants are required to disclose multiple examples of particular modified plant zinc finger proteins[4], as well as methods of making additional modified plant zinc finger proteins as claimed is inconsistent with the requirements of the first paragraph of Section 112.

Moreover, Applicants also amply describe that which is new, *i.e.*, modifying plant zinc finger proteins as claimed. Thus, the disclosure of the specification as filed more than satisfies the written description requirement with the respect to the pending claims; and the notion that the specification describes "only a single genus of polynucleotides ...derived from the *Arabidopsis* zinc finger sequences of SEQ ID NOs:13 and 14 and one derived from the petunia zinc finger sequence of SEQ ID NO:12," is inconsistent not only with *Capon* but with every case, rule and guideline relating to the written description requirement.

As shown above, literal description is present in the original claims and description; therefore the written description requirement has been satisfied. Applicants have shown possession of the claimed molecules at the time of filing – clearly and unmistakably. The written description inquiry need go no further than the claims and text of the specification itself, which clearly evinces possession of the subject matter of as claimed.

35 U.S.C. 112, FIRST PARAGRAPH, ENABLEMENT

Claims 10 and 31 stand rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not enabled by the specification as filed. In particular, it was asserted that the specification does not teach one of skill in the art how to practice make or use any "non-canonical" zinc finger protein. (Office Action, pages 6-7).

Applicants traverse the rejection and supporting remarks.

The test of enablement is whether one reasonably skilled in the art could practice the claimed methods, using the disclosures in the specification coupled with information known in the art, without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

[4] over and above the 17 examples already provided; *see* Tables 1 and 2

Furthermore, a patent application is presumptively enabled upon filing and is incumbent upon the Patent Office to explain why it doubts the truth or accuracy of any statements in the disclosure. *In re Marzocchi*, 439 F.2d, 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Applying these rules to the pending case, Applicants submit that the specification provides ample guidance on the physical properties of the zinc finger proteins, including the non-canonical structure of the binding motifs set forth claims 10 and 31. *See, e.g.*, page 10, line 25 through page 11, line 2, wherein the term "non-canonical" is defined. The term "non-canonical" thus clearly refers to a zinc finger protein in which one or more of the canonical zinc-coordinating residues (Cys-Cys-His-His) is replaced with a different residue and this definition is well known to those of skill in the art.

Furthermore, the skilled artisan would know how to make and use non-canonical zinc fingers so as to retain their binding functionality. Indeed, any alterations (for example to engineer the non-canonical finger to bind to a selected target site) would be utterly routine to the skilled artisan in view of the detailed disclosure in the specification regarding such engineering. Thus, the Office has not (and indeed cannot) present evidence reasonably establishing that these zinc finger proteins are not enabled by the specification as filed.

With respect to the comments in the Office Action that there is insufficient guidance regarding how to modify plant zinc fingers including non-canonical zinc fingers, Applicants direct the Examiner's attention to pages 17-21 and the Examples, where the specification teaches how to modify any plant zinc finger protein so as to bind to a target site and teaches how to reduce the spacing between naturally-occurring plant zinc fingers.

Applicants also remind the Office that a specification need not teach and preferably omits that which is known to those working in the field. *See, e.g., Loom Co. v. Higgins*, 105 U.S. 580, 585-86 (1882); *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) and *In re Gay*, 309 F.2d 769, 774 (CCPA 1962) pointing out that "not every last detail [of an invention need] be described [in a specification], else patent specifications would turn into production specification, which they were never intended to be." At the time of filing, engineering of zinc finger proteins to bind to a particular target site was described in the art, for example in U.S. Patent No. 6,824,978 (cited in the Office Action and discussed below), as were non-canonical zinc fingers (*see*, for example, US Patent Application Publication No. 2003/0108880). Therefore, the specification, in view of

the state of the art at the time of filing, evidences that non-canonical zinc fingers, as defined in the present specification, as well as methods of modifying zinc finger proteins, were sufficiently disclosed to the skilled artisan.

Therefore, the Office's assertion that "trial and error" is required to make and use zinc finger proteins as set forth in claims 10 and 31 is untenable. The specification teaches how to make and use proteins including non-canonical zinc fingers as well as how to modify naturally occurring plant zinc finger proteins and, accordingly, the skilled artisan would know that a non-canonical finger could be readily engineered to bind to a particular target site.

In summary, a modified plant zinc finger protein in which at least one zinc finger of the tandem array comprises a non-canonical zinc finger protein that has been engineered to bind to a target site are fully enabled by the specification as filed. Non-canonical zinc fingers as well as methods of engineering any (canonical or non-canonical) zinc finger were well-known to those of skill in the art as of the filing date, and thus need not be disclosed in the specification in any more detail than they are. Accordingly, the specification as filed fully enables the claims throughout their scope.

35 U.S.C. 112, SECOND PARAGRAPH

Claim 21 was rejected under 35 U.S.C. 112, second paragraph as allegedly indefinite for lack of antecedent basis for the recitation "the modification." (Office Action, page 7).

Applicants submit that the recitation in previous claim 21 regarding "the modification" plainly referred to how the modified plant zinc finger proteins are modified. Nonetheless, solely to expedite prosecution, the claim has been amended as shown above to obviate the rejection. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph may be withdrawn.

35 U.S.C. § 102/103

Claims 1-4, 6-9, 11, 17-19, 21-30 and 32 were rejected as allegedly anticipated or obvious over U.S. Patent No. 6,140,466 (hereinafter "Barbas"). (Office Action, pages 10-13). It was alleged that the fact that the zinc fingers are derived from two or more plant species does not distinguish the claimed proteins from those of Barbas.

As a threshold matter, Applicants request that, if the rejection is maintained, it be clarified as either an anticipation rejection or an obviousness rejection, so that Applicants can properly evaluate the relevant criteria and present an appropriate response.

As acknowledged by the Office, Barbas teaches only proteins comprising Cys2-His2 zinc fingers in which the backbone is derived from a non-plant ZFP, namely murine Zif268 or amphibian (*Xenopus*) TFIIIA. Pending claims 1-4, 6-9, 11, 17-19 exclude proteins whose backbones are derived from Zif268 or TFIIIa. Thus, Barbas's proteins differ in sequence from those claimed and, inasmuch as the Office takes the position that sequence is identical to structure, they differ in structure as well.

For their parts, claims 21-30 and 32 are directed to modified plant zinc fingers and specify that the proteins are modified in the recognition region. In other words, the claimed proteins have naturally occurring plant ZFP sequences in their backbone and engineered (non-naturally-occurring) sequences in the target-binding regions. In contrast, Barbas discloses only proteins with mouse ZIF268 and amphibian TFIIIA backbones. Thus, the proteins of claims 21-30 and 32 are distinguishable in sequence from those disclosed by Barbas and, inasmuch as the Office takes the position that sequence is identical to structure, they differ in structure as well. Accordingly, withdrawal of the rejection is in order.

35 U.S.C. § 103

Claims 14 and 33 were rejected under 35 U.S.C. § 103 as allegedly obvious over Barbas in view of U.S. Patent No. 6,706,470 (hereinafter "Choo"). (Office Action, pages 13-14).

Claims 14 and 33 depend from claims 1 and 21 respectively. For the reasons noted above, Barbas's disclosure of canonical Cys2-His2 zinc fingers with non-plant backbones does not teach or suggest the subject matter of claims 1 and 21. Accordingly, claims 14 and 33 are not obvious over Barbas, alone or in combination with Choo, and the rejection may be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance and request early notification to that effect. If the Examiner has any further issues or wishes to discuss any of the foregoing, they are invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

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